care, and there must be a total physical therapy program by therapists experienced with this type of patient. Septic complications of intravenous catheters must be prevented, and we try to avoid urethral catheters by using external drainage systems. Since gastric stress ulceration and bleeding is a significant cause of morbidity and mortality in tetanus and botulism, it is wise to institute prophylactic antacid therapy. Cimetidine may prove to be of additional value. A complete nutritional diet including vitamins, trace elements and minerals is necessary and fluids and electrolytes must be balanced meticulously.

The physician and nurses must be forewarned and prepared for autonomic dysfunction especially in cases of tetanus,[54,57,60] predominantly manifested as arrhythmias, tachycardia, labile blood pressure, hyperpyrexia, and excessive sweating and salivation.

Clostridia, in addition to the ability to cause neuromuscular disease noted above, also cause a spectrum of skin and soft tissue infections. The final segments of this symposium deal with these emergencies and the appropriate management of these syndromes.

Skin and Soft Tissue Infections

PHILLIP J. RAIMONDI, MD*

IN ADDITION to their etiologic roles in tetanus and botulism, clostridia are probably best known for their ability to cause myonecrosis or gas gangrene. It should be remembered, however, that this dramatic syndrome is uncommon and represents the far end of a broad spectrum of clostridial disease ranging from the benign to the fulminant and frequently lethal. In addition, clostridia are frequently harmless colonizers and therefore a culture report from any source showing clostridia must be interpreted in light of the clinical setting.[61,62]

Infections Other Than Gas Gangrene

Numerous clostridial species have been isolated from many different primary sites of infection (Table 6). Since these organisms are normal inhabitants of the human bowel, their presence in intraabdominal infection is not surprising.[63] The frequency with which they have been recovered is variable, however. Clostridia accounted for only eight of 198 (3.6 percent) anaerobic isolates in a group of patients with peritonitis or intraabdominal abscess studied by Lorber and Swenson.[64] On the other hand, in a similar group of patients with peritonitis or intraabdominal abscess reported by Finegold and associates clostridia were second in frequency only to bacteroides species and accounted for 43 of 173 (25 percent) anaerobic isolates.[65] Intraabdominal infection is typically polymicrobial and it should be noted that only rarely are clostridia isolated in pure culture.[65] The question then arises as to the importance of clostridia relative to the other organisms isolated in these infections. Certainly, overwhelming clostridial infection is an uncommon complication of intraabdominal sepsis suggesting that although clostridia may commonly be isolated along with other bacteria, they usually do not assume any special or unique importance. A similar statement can be made with regard to pelvic abscess. Clostridia may be present in such abscesses but subsequent severe clostridial sepsis is uncommon.[66]

TABLE 6.—*Clostridial Species Isolated from Human Infections*

Clostridium barayi	Clostridium limosum
Clostridium beijerinckii	Clostridium multifermentans
Clostridium bifermentans	Clostridium perfringens
Clostridium botulinum	Clostridium pseudotetanicum
Clostridium butyricum	Clostridium putrificum
Clostridium cadivaris	Clostridium ramosum
Clostridium capitovale	Clostridium septicum
Clostridium carnis	Clostridium sordelii
Clostridium difficile	Clostridium sphenoides
Clostridium fallax	Clostridium sporogenes
Clostridium ghoni	Clostridium subterminale
Clostridium hastiforme	Clostridium tertium
Clostridium innocuum	Clostridium tetani

Clostridial species, most notably C perfringens, have been isolated from the bile in as many as 19 percent to 20 percent of patients undergoing biliary tract surgical procedures.[67,68] Resulting clostridial sepsis or extensive soft tissue infection (or both) may develop in this setting, but fortunately are uncommon. A somewhat special circumstance may be so-called emphysematous cholecystitis. This is an uncommon form of acute cholecystitis characterized by the presence of gas in the gallbladder. Clostridia (usually C perfringens) are isolated in close to half of the cases.[67] In one series, gangrene or perforation of the gallbladder (or both) occurred in three fourths of the cases and the mortality rate was considerably higher than that of nonemphysema-

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tous cholecystitis.[67] Whether or not clostridia play a primary pathogenic role in this disease is an unsettled issue.

Clostridial organisms uncommonly cause pleuroplumonary infection. Bartlett and co-workers[69] and Lorber and Swenson[70] recovered clostridia from patients with aspiration pneumonia in only five of 54 (9 percent) and none of 47 cases, respectively. In none of Bartlett's cases were the clostridia in pure culture. Similarly, in cases of lung abscess and anaerobic empyema, clostridia are rarely isolated. Clostridial pneumonia and empyema have been reported following thoracotomy[71] and penetrating chest trauma.[72] Recently, Bayer and associates[73] reviewed C perfringens pneumonia and empyema. In seven of the 11 cases reviewed, the clostridial infection was preceded by an invasive chest procedure such as thoracentesis or chest tube insertion. It appears then that the pathogenesis of most pure clostridial pleuropulmonary infection involves introduction of organisms either by trauma or an invasive medical procedure.

Clostridia, either alone or in mixed culture, have rarely been isolated from a variety of other infections including osteomyelitis,[74] meningitis,[75] brain abscess,[76] subcutaneous abscesses[76] and spontaneous peritonitis.[77] Cellulitis can be caused by clostridia, usually C perfringens. This infection may complicate traumatic wounds and can coexist with clostridial myonecrosis.[77,79] Differentiation between the two diseases is important because of the need for more extensive surgical therapy in the latter disease.[78] Excessive gas formation with obvious crepitance is more common in cellulitis than in myonecrosis and may serve as a distinguishing feature.[79] Also, patients with clostridial cellulitis generally do not manifest the marked systemic toxicity characteristically seen in patients with myonecrosis.[79]

Gas Gangrene

The term gas gangrene refers specifically to clostridial myonecrosis. This disease was a major problem during the two world wars primarily because of inadequate early surgical management of traumatic wounds.[61] In civilian life, gangrene is still seen following trauma but it also occurs in patients with peripheral vascular disease, malignancy and a variety of intraabdominal disorders, and in obstetrical patients.

The organisms involved are the histotoxic strains of clostridia, so called because of their ability to produce exotoxins capable of tissue destruction. C perfringens has been the most common offender but C novyi, C septicum and several others can also cause gangrene (Table 7).[61] Of these, phospholipase C, or the so called alpha toxin, is felt to be the most important clinically, and is probably responsible for much of the tissue destruction seen in gas gangrene.[61]

TABLE 7.—*Histotoxic Clostridia*

Clostridium perfringens	Clostridium histolyticum
Clostridium novyi	Clostridium bifermentans
Clostridium septicum	Clostridium fallax

Intravascular hemolysis with spherocytes in the peripheral blood, intravascular coagulation and renal failure can be seen with severe clostridial infection.[61,80-82] The alpha toxin causes hemolysis in experimental animals[61] and has been proposed as the cause of hemolysis in man. Indeed, activity attributable to this substance has been identified in the blood of a patient with clostridial sepsis and hemolytic anemia.[83] Studies of the cell membranes from a patient with clostridia-induced hemolysis, however, showed major changes in the protein moiety, indicating that a factor other than phospholipase C may be of major importance.[84]

The cause of the intravascular coagulation has not been determined. Products of red cell destruction and damage to vascular endothelium by exotoxins have been proposed as inciting factors.[81]

The renal lesion is usually acute tubular necrosis and much less commonly cortical necrosis. A specific nephrotoxin has not been identified.

Gas gangrene secondary to trauma most frequently involves an extremity.[85] It may follow minor injuries[61] but usually develops in severe wounds with extensive muscle damage.[61,78] The vascular supply to the area may be impaired and the wounds are frequently contaminated by clothing, dirt or foreign bodies. Initial surgical management is often found to have been inadequate or delayed.[61,86] Such wounds provide an appropriate anaerobic environment for conversion of clostridial spores to vegetative forms and for growth of the vegetative forms. Exotoxins are produced, resulting in destruction of muscle. Variable amounts of gas may be produced and, in conjunction with edema fluid, result in increased local pressure and impairment of vascular supply and drainage. Further necrosis results,

creating additional areas appropriate for clostridial growth and the infection thereby spreads.

The period between time of injury and onset of symptoms ranges from hours to weeks but is usually a few days.[78,80] Severe pain is the earliest symptom followed shortly by tachycardia which, if present, is frequently out of proportion to what may be only low grade fever.[78] The primary wound is generally not pyogenic in appearance and the surrounding skin may initially appear normal or has been described as white, shiny and tense.[78] Crepitance is uncommon in early gangrene and may be minimal even in later stages. Excessive gas in tissues, in fact, should suggest another diagnosis such as clostridial cellulitis.[79,80] The wound itself may exude a watery brown discharge, the odor of which has been variably described as either sweet or foul.[78,79] This discharge typically contains red cells and clostridial organisms but very few polymorphonuclear leukocytes.[80,87] In the later stages, swelling in the area increases and the surrounding skin may become bronzed, deep burgundy, brown or even black in color. Large cutaneous vesicles develop, filled with serosanguinous fluid, again containing few polymorphonuclear leukocytes. This stage of the illness is characterized by severe systemic toxicity and possible hypotension. Renal failure may develop, as well as hemolytic anemia; however, the latter is more commonly seen with uterine infections rather than those following trauma.[61] Bacteremia is seemingly uncommon having been found in only 15 percent of cases by Caplan[85] and 13 percent of cases by Duff and associates.[88]

There may be diagnostic confusion between gas gangrene and a number of other soft tissue infections. These include clostridial cellulitis, streptococcal myositis and synergistic necrotizing cellulitis caused by an aerobic Gram-negative rod such as Klebsiella or E coli in combination with anaerobic streptococci or Bacteroides species.[78,79] Showing the presence of clostridia within a wound by Gram stain or culture does not establish the diagnosis of gas gangrene, however. Clostridia contaminate a high percentage of extensive traumatic wounds yet gangrene develops in very few.[78] Examination of muscle, therefore, is mandatory in order to make the proper diagnosis. Early in clostridial myonecrosis, the muscles are hemorrhagic and friable. Later, there is loss of contractibility, absence of bleeding from the cut surface and what has been described as a brick-red discoloration.[80] Gas may be grossly visible. Histologically, one sees edema, loss of normal muscle striations and eventual liquefactive necrosis of muscle. Clostridia are abundant within the necrotic muscle but there is minimal polymorphonuclear infiltration except at the periphery of the lesion.[90]

Patients with vascular insufficiency in whom gangrene develops are usually elderly and frequently have diabetes mellitus. A cutaneous ulcer may be present, but at times there is not an obvious primary lesion. Presumably, clostridia are introduced into the tissues by minor trauma and the ischemic environment permits proliferation. The pathogenesis is then similar to those cases precipitated by trauma.

Clostridial myonecrosis has also been reported as a postoperative complication of vascular surgical procedures or amputation of an ischemic extremity.[89,90]

There have been a number of reports of severe clostridial infection in patients with cancer.[91-97] The most common malignant lesions have been leukemia and gastrointestinal carcinoma, but patients with many other types of tumors have also been reported.[97] It has been postulated that the milieu within solid tumors is favorable to the growth of clostridia.[93,96] Indeed, as cited by Alpern and Dowell,[94] and Propst and Möse,[98] there have been instances of avirulent clostridia injected into patients with terminal malignancy. The organisms germinated only within tumor tissue resulting in liquefactive necrosis to tumor but not normal tissue.

A common finding in patients with cancer and clostridial infection has been disruption of the integrity of the intestines either by carcinoma, leukemic infiltrates or a nonneoplastic process. In patients with leukemia, clostridial bacteremia without extensive soft tissue infection has been most commonly reported but extensive myonecrosis can also occur.[94,97] This may involve primarily the bowel wall[93] or a distant area such as an extremity, usually without notable external trauma. Presumably, bacteremia arises from the bowel and a distant focus is seeded. Depressed host defenses, possibly coupled with minor focal trauma, permit proliferation of the clostridia and resulting gangrene.

Colon cancer is the most common gastrointestinal malignant condition complicated by clostridial infection. Such infections may develop with or without preceding perforation and abscess formation and can occur postoperatively follow-

ing resection of a carinoma. There may be bacteremia alone or extensive myonecrosis involving the retroperitoneal and anterior abdominal muscles. Extension into the thigh has been reported on several occasions.[95,99]

Gas gangrene is an uncommon complication of a number of intraabdominal disorders other than cancer. These include cholecystitis, penetrating duodenal ulcer, intestinal perforation, and perirectal or scrotal abscesses.[85,100-102] Gangrene has also been a complication of decubitus ulcers[103] and may follow many types of abdominal surgical operations including appendectomy, large or small bowel resection, gastrectomy, cholecystectomy and hemorroidectomy.[91,92,103] The muscles most commonly involved are those of the anterior abdominal wall and perineum. Occasionally, the retroperitoneum is involved and, rarely, the gangrene is localized to an extremity far removed from the site of the primary disease process or the operative wound.[101] The onset of illness is heralded by an abrupt worsening of the patient's condition. Either drowsiness or agitation may be the earliest changes with associated tachycardia, fever and later hypotension. Icterus due to intravascular hemolysis and deteriorating renal function are occasionally present. Increasing severe abdominal pain develops in some but not all cases. Tan or bluish discoloration of the skin overlying the area of myonecrosis has been described as the earliest local physical finding.[91] Crepitance may then develop but is often not pronounced. The process may spread quite rapidly and unless therapy is promptly instituted, will terminate in extensive myonecrosis, shock and death.

Clostridial infection in obstetrical patients is usually seen following abortion and fortunately is uncommon.[104] As pointed out by Smith,[81] these organisms may be present in the genital tract of 19 percent to 27 percent of aborting patients.[105,106] Eaton and Peterson,[108] however, found that clostridia were significant pathogens in only seven of 430 (1.7 percent) septic abortions. Once clostridia have been identified in the blood or genital tract, one is faced with the problem of distinguishing between colonization, benign transient disease and life-threatening infection. Ramsay, for example, reported about 28 patients with postabortal C perfringens bacteremia, 17 of whom had benign disease with minimal systemic toxicity.[104] Intrauterine clostridial infection may lead to typical features of sepsis, however, with fever, chills and hypotension. This disease clearly requires therapy and has been successfully treated with administration of penicillin and uterine evacuation.[107] The most devastating form of postabortal clostridial disease is myonecrosis or gangrene of the myometrium with so called "septicotoxemia." In its fullest proportions, this syndrome consists of the rapid development of pronounced systemic toxicity with brisk hemolysis, jaundice and hemoglobinuria, coagulation abnormalities, renal failure and shock. Lower abdominal pain and tenderness may be severe and gas within the uterine wall may be visible on x-ray films. The presence of severe hemolysis is considered a poor prognostic sign. Since the infection extends beyond the endometrium, simple uterine curettage is not considered adequate therapy for this condition.[108] Bilateral salpino-oophorectomy and hysterectomy appears to be the operation of choice and is probably the most important aspect of therapy.[107,108] Fluid replacement and blood transfusion are frequently necessary for shock and anemia. Penicillin in doses of 20 million units per day is the antibiotic of choice[6] with chloramphenicol being an alternative agent for penicillin-sensitive patients. Other treatment modalities such as heparin for intravascular coagulation, hyperbaric oxygen and clostridial antitoxin are of unproven value.[107,108]

Clostridial Bacteremia

A final note should be added about clostridial bacteremia. Clostridia may invade the blood from many if not all of the primary infections just reviewed. Even if histotoxic clostridia are involved, the clinical findings are quite variable. There may be little clinical evidence of septicemia as noted by Ramsay;[104] there may be shock indistinguishable from that caused by any other microorganisms; or, there may be fulminant septicotoxemia. The severity of the primary infection rather than bacteremia alone may be an important determinant of the clinical features. Although there are exceptions, most patients in whom severe hemolysis or coagulation abnormalities associated with clostridial bacteremia develop have an extensive underlying soft tissue infection. Furthermore, in the occasional patient with sterile blood cultures hemolysis may develop presumably from toxins liberated into the blood directly from the primary focus of infection.[104]

Another interesting aspect of clostridial bacteremia is that it may arise in seemingly unrelated

clinical settings. Alpern and Dowell,[109] for example, reported on patients with nonhistotoxic clostridial bacteremia whose underlying diseases included various pulmonary disorders, congestive heart failure, bleeding peptic ulcer, cirrhosis and iron deficiency anemia. The bacteremia was seemingly benign in some cases since ten of 12 patients who did not receive antibiotics survived. Gorbach and Thadepalli[76] also made this observation in their patients at Cook County Hospital. They were able to evaluate 29 patients with blood cultures positive for clostridia including some histotoxic strains. Whereas twelve of the 29 patients had soft tissue infections involving clostridia, a number of patients had underlying diseases not usually associated with clostridial infection. These include six patients with aspiration pneumonia, two with cavitary tuberculosis, two with a seizure disorder and one with meningococcemia. Why clostridial bacteremia should develop in these patients is an interesting but unanswered question.

Management of clostridial soft tissue infection is as varied as the infectious syndromes these agents may cause. Appropriate drainage of focal infection and administration of penicillin are the cornerstones of therapy. With more serious infection, aggressive therapeutic intervention is indicated.

Therapy of Clostridial Myonecrosis

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SUCCESSFUL THERAPY of patients with clostridial myonecrosis depends in great measure on the general state of health of the patient and the rapidity with which the diagnosis is made. Delay in the initiation of therapy may yield catastrophic results.[62]

Appropriate surgical management of clostridial myonecrosis includes several therapeutic modalities. While the relative importance of each of the following aspects of treatment remains a topic of controversy, many authorities agree that combinations of (1) surgical debridement, (2) antibiotic therapy, (3) hyperbaric oxygen and (4) supportive measures are necessary. The administration of polyvalent antitoxin has not been shown to be effective, and many centers have discontinued use of the antitoxin because of the risk of hypersensitivity phenomena.[110]

Surgical debridement is included by virtually all authors as a cornerstone of therapy. The time of operation and extent of debridement is less clear. Altemeier suggests wide, emergent debridement with multiple incisions and appropriate fasciotomies.[62] Roding and co-workers recommended limiting emergent surgical therapy to opening the original wound and incising abscesses.[111] These authors suggest delaying definitive surgical procedures until demarcation of necrosis occurs, with the hope of limiting disfigurement.[111] Early surgical intervention not only may allow decompression but also, as noted above, facilitates early diagnosis.

The role of antibiosis is somewhat less clear. The drug of choice is aqueous pencillin in doses of 20 million units per day. While the efficacy of penicillin is difficult to delineate, animal models have suggested the beneficial effect of antibiotics.[112] Second line drugs, to be used in patients allergic to penicillin, include cephalosporins, chloramphenicol and erythromycin. Sensitivity testing is advisable, especially if tetracycline, another macrolide, clindamycin or carbenicillin is being used.[111]

Hyperbaric oxygen has been shown to decrease mortality, and has been suggested to limit tissue necrosis. Positive results using hyperbaric oxygen have been obtained from several laboratories.[111-114] In an experimental study, Demello and co-workers showed the value of 100 percent oxygen at three atmospheres, but also showed that for maximum effectiveness in their model, debridement and antibiotics should be used.[112]

Supportive measures should include careful medical management as well as anticipation and prompt therapy of complications of clostridial bacteremia.

Management of these patients frequently involves volume expansion with intravenous fluid, plasma and blood. Shock is a frequent complication and rapid volume expansion may be necessary. Monitoring central venous pressure or (more reliably) pulmonary capillary wedge pressure may be of value in severely ill patients. The role of steroids remains somewhat controversial. Additionally, careful monitoring of the electrolytes and packed cell volume may avert potential com-

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